PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 263/58, 213/74, 239/42, A61K 31/42 — A1

(11) International Publication Number: WO 95/17394

(43) International Publication Date: 29 June 1995 (29.06.95)

(21) International Application Number: PCT/EP94/04112

(22) International Filing Date: 10 December 1994 (10.12.94)

(30) Priority Data:
9326171.7 22 December 1993 (22.12.93) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CANTELLO, Barrie, Christian, Charles [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). HAIGH, David [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: HETEROCYCLIC DERIVATIVES AND THEIR USE IN PHARMACEUTICALS

(57) Abstract

A compound of the formula (I): $A^1—X—(CH_2)_n—O—A^2—A^3—Y$ or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein: A^1 represents a substituted or unsubstituted aromatic heterocyclyl group; A^2 represents a benzene ring having three optional substituents; A^3 represents a moiety of formula $-(CH_2)_m-CH(OR^1)-$ wherein m represents an integer in the range of from 1 to 5 and R^1 represents a moiety $-(CH_2)_x-Y^1-(CH_2)_y-T$ wherein Y^1 represents O, NR^o wherein R^o is H, alkyl or alkylcarbonyl or Y^1 is S, T represents a phenyl group optionally substituted with up to 3 substituents selected from halo, alkyl and alkoxy, x represents an integer in the range of from 2 to 5 and y represents zero or an integer in the range of from 1 to 5; or A^3 represents a moiety of formula $-(CH_2)_{m-1}-CH=C(OR^1)-$ wherein R^1 and m are as defined above; R^2 represents OR^3 wherein R^3 represents hydrogen, alkyl, aryl or aralkyl or R^2 represents an aromatic heterocyclyl group or $-NR^4R^5$ wherein R^4 and R^5 each independently represent hydrogen, alkyl or alkylcarbonyl or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring, providing that R^2 represents an aromatic heterocyclyl group only when Y as defined below represents a bond; X represents NR wherein R represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; Y represents C=O or C=S or a bond providing that Y represents a bond only when R^2 represents the above mentioned aromatic heterocyclyl group; and n represents an integer in the range of from 2 to 6; a process for preparing such a compound, a composition comprising such a compound and the use of such a compound and composition in medicine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

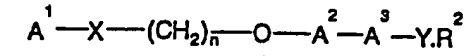
HETEROCYCLIC DERIVATIVES AND THEIR USE IN PHARMACEUTICALS

This invention relates to certain novel compounds, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

It has now surprisingly been discovered that certain novel compounds show particularly good blood-glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and are of particular use in the treatment of Type II diabetes.

These compounds are also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia and hypertension. They are also indicated to be of use in the treatment and/or prophylaxis of cardiovascular disease, especially atherosclerosis. In addition these compounds are considered to be useful for treating certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating ,such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia.

Accordingly, the present invention provides a compound of formula (I):



(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

A^2 represents a benzene ring having three optional substituents;

A^3 represents a moiety of formula $-(CH_2)_m-CH(OR^1)-$ wherein m represents an integer in the range of from 1 to 5 and R^1 represents a moiety $-(CH_2)_x-Y^1-(CH_2)_y-T$ wherein Y^1 represents O, NR° wherein R° is H, alkyl or alkylcarbonyl or Y^1 is S, T represents a phenyl group optionally substituted with up to 3 substituents selected from halo, alkyl and alkoxy, x represents an integer in the range of from 2 to 5 and y represents zero or an integer in the range of from 1 to 5; or

A^3 represents a moiety of formula $-(CH_2)_{m-1}-CH=C(OR^1)-$ wherein R^1 and m are as defined above;

R^2 represents OR^3 wherein R^3 represents hydrogen, alkyl, aryl or aralkyl or R^2 represents an aromatic heterocyclyl group or $-NR^4R^5$ wherein R^4 and R^5 each independently represent hydrogen, alkyl or alkylcarbonyl or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring, providing that R^2 represents an aromatic heterocyclyl group only when Y as defined below represents a bond ;

X represents NR wherein R represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

Y represents C=O or C=S or a bond providing that Y represents a bond only when R^2 represents the above mentioned aromatic heterocyclyl group; and

n represents an integer in the range of from 2 to 6.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

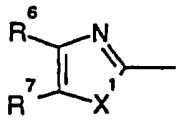
Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 5 to 7 ring atoms, preferably 5 or 6 ring atoms.

In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

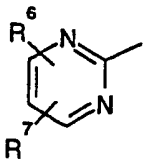
Suitable values for A^1 when it represents a 5- membered aromatic heterocyclyl group include thiazolyl and oxazolyl, especially oxazolyl.

Suitable values for A^1 when it represents a 6- membered aromatic heterocyclyl group include pyridyl or pyrimidinyl, especially pyridyl.

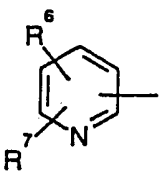
Preferably, A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

wherein:

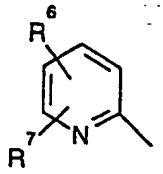
R^6 and R^7 each independently represents a hydrogen or halogen atom, an alkyl or alkoxy group or a substituted or unsubstituted aryl group or when R^6 and R^7 are each attached to adjacent carbon atoms, then R^6 and R^7 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^6 and R^7 together is substituted or unsubstituted; and in the moiety of formula (a) X^1 represents oxygen or sulphur.

Aptly, A^1 represents a moiety of the abovedefined formula (a).

Aptly, A^1 represents a moiety of the abovedefined formula (b).

Aptly, A^1 represents a moiety of the abovedefined formula (c).

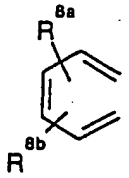
A particular form of moiety (c) is a moiety (c'):



(c')

wherein R^6 and R^7 are as defined in relation to formula (c).

In one favoured aspect R^6 and R^7 together represent a moiety of formula (d):



(d)

wherein R^{8a} and R^{8b} each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^{8a} and R^{8b} each independently represent hydrogen, halogen, alkyl or alkoxy. Favourably, R^{8a} represents hydrogen. Favourably, R^{8b} represents hydrogen. Preferably, R^{8a} and R^{8b} both represent hydrogen.

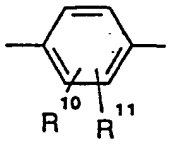
In a further favoured aspect R^6 and R^7 each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group and more favourably, R^6 and R^7 each independently represent hydrogen, alkyl or phenyl.

Preferably, for the moiety of formula (a), R^6 and R^7 together represent the moiety of formula (d).

Preferably, for the moieties of formula (b), (c) or (c'), R^6 and R^7 both represent hydrogen.

Optional substituents for A^2 are selected from the group consisting of: halogen, substituted or unsubstituted alkyl and alkoxy.

Favourably, A^2 represents a moiety of formula (e):



(e)

wherein R^{10} and R^{11} each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^{10} and R^{11} each independently represent hydrogen, halogen, alkyl or alkoxy.

When R^{10} or R^{11} represent alkoxy, a suitable alkoxy group is a methoxy group.

Preferably, R^{10} and R^{11} each represent hydrogen.

Suitably, A3 represents a moiety of formula $-(CH_2)_m-CH(OR^1)-$.

Suitably, A^3 represents a moiety of formula $-CH=C(OR^1)-$.

Suitably, x represents 2.

An example of y is 1.

Suitably y represents zero.

Suitably, Y^1 represents O.

Suitably, T represents phenyl.

Favourably, R^1 represents a moiety of formula $-CH_2-CH_2-O$-phenyl.

Suitably, R^3 represents hydrogen or alkyl.

When R^3 is alkyl, examples of R^3 include methyl and ethyl.

When R^2 is an aromatic heterocyclyl group it is suitably a single ring aromatic heterocyclyl group having 5 ring atoms, which ring atoms comprise nitrogen and optionally 1, 2 or 3 additional hetero atoms; examples include 1, 2, 4-triazole; 1, 2, 4- oxadiazole and tetrazolyl; generally the aromatic heterocyclyl group is C-linked.

Suitable substituents on the aromatic heterocyclyl group include alkyl, aryl, alkoxy and halo, an example of a substituent is methyl.

When $-NR^4R^5$ or $-NR^sR^t$ represents a heterocyclic ring, favoured heterocyclic rings are saturated or unsaturated, fused or monocyclic heterocyclic rings comprising 5, 6 or 7 ring atoms and optionally comprising 1 or 2 additional hetero-atoms, selected from O,S or N, in each ring. Favoured rings are saturated rings. Favoured rings are monocyclic rings. Favoured, additional hetero-atoms are N or O. Examples of such heterocyclic rings include N- pyrrolidinyl, N-piperidinyl and N-morpholinyl.

A further example of NR^4R^5 is NH_2.

Suitably, R^2 represents NR^4R^5.

Preferably R^2 is OR^3.

Suitably when R^2 represents OR^3 wherein R^3 represents hydrogen, alkyl, aryl or aralkyl or R^2 represents $-NR^4R^5$, Y is CO or CS; preferably, Y is CO.

When R^2 is an aromatic heterocyclyl group, Y is a bond.

Suitably, R represents hydrogen or alkyl.

When R is acyl, suitable acyl groups include alkylcarbonyl groups, such as acetyl.

Suitably, m represents 1 or 2.

Favourably, m is 1.

Favourably, n is 2.

As indicated above, a compound of formula (I), and the pharmaceutically acceptable salts thereof, may exist in one of several tautomeric forms, all of which are encompassed by the present invention as individual tautomeric forms or as mixtures thereof. The compounds of formula (I) may contain at least one chiral carbon, and hence they may exist in one or more stereoisomeric forms. For example, when A^3 represents a moiety of formula $-(CH_2)_m-CH(OR^1)-$ the $CH(OR^1)$-carbon atom is a chiral carbon. In addition, when A^3 represents a moiety of formula

$-(CH_2)_{m-1}-CH=C(OR^1)-$ the compounds of formula (I) exist as geometric isomers. The present invention encompasses all of the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, whether as individual isomers or as mixtures of isomers, including racemates.

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a phenylene group, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein, unless otherwise stated, the term 'aryl' includes phenyl and naphthyl; any aryl group mentioned herein may be optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

As used herein, alkyl groups, whether present alone or as part of other groups such as alkoxy or aralkyl groups, are alkyl groups having straight or branched carbon chains, containing up to 12 carbon atoms. Thus, suitable alkyl groups are C_{1-12} alkyl groups, especially C_{1-6} alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Favoured aralkyl groups are phenylalkyl groups, optionally substituted on the aryl or alkyl moieties as defined herein.

Suitable acyl groups include alkylcarbonyl groups

Suitable pharmaceutically acceptable salts include salts of carboxy groups and acid addition salts.

Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine,

cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphonate, α-keto glutarate and α-glycerophosphate.

Suitable pharmaceutically acceptable solvates include hydrates.

The salts and/or solvates of the compounds of formula (I) may be prepared and isolated according to conventional procedures for example sodium salts may be prepared by using sodium methoxide in methanol.

In a further aspect the present invention also provides a process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, which process comprises reacting a compound of formula (II):

(II)

wherein A^2 and Y are as defined in relation to formula (I);
$A^{3'}$ represents a moiety of formula $-(CH_2)_m-CH(OR^{1'})-$ wherein $R^{1'}$ represents R^1 as defined in relation to formula (I) or a protected form thereof, and m is as defined in relation to formula (I), or A^3 represents a moiety of formula $-(CH_2)_{m-1}-CH=C(OR^{1'})-$ wherein $R^{1'}$ is as defined above;
$R^{2'}$ represents R^2 as defined in relation to formula (1) or a protected form thereof and R^a is a moiety convertible to a moiety of formula (f):

$$A^1\text{-}X\text{-}(CH_2)_n\text{-}O- \qquad (f)$$

wherein A^1, X and n are as defined in relation to formula (I);

with an appropriate reagent capable of converting R^a to the said moiety (f) and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

Suitably, R^a represents $HX\text{-}(CH_2)_n\text{-}O\text{-}$ wherein X and n are as defined in relation to formula (I), or R^a represents OH.

Preferably, R^a represents OH.

When R^a is $HX\text{-}(CH_2)_n\text{-}O\text{-}$, an appropriate reagent capable of converting R^a to a moiety (f) is a compound of formula (III):

$$A^1 - R^X \qquad \text{(III)}$$

wherein A^1 is as defined in relation to formula (I) and R^X represents a leaving group.

A suitable leaving group R^X includes a halogen atom, preferably a chlorine or bromine atom, or a thioalkyl group for example a thiomethyl group.

Generally, $R^{1'}$ is R^1. Preferably, $R^{2'}$ represents $OR^{3'}$ wherein $R^{3'}$ represents hydrogen, alkyl, aryl, aralkyl or $R^{2'}$ represents the above defined moiety $-NR^4R^5$.

When R^a is OH, an appropriate reagent is a compound of formula (IIIA):

$$A^1\text{-}X\text{-}(CH_2)_n\text{-}OR^Y \qquad \text{(IIIA)}$$

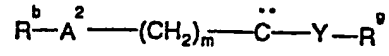
wherein A^1, X and n are as defined in relation to formula (I) and R^Y represents a leaving group, such as a tosylate or mesylate group.

The reaction between the compound of formula (II) and the appropriate reagent may be carried out under conditions suitable to the particular compound of formula (II) and the reagent chosen: For example the abovementioned reaction between a compound of formula (II) wherein R^a represents $HX\text{-}(CH_2)_n\text{-}O\text{-}$ and the compound of formula (III), may be carried out in any suitable solvent, for example dimethylformamide, at a temperature which provides a suitable rate of

formation of the compound of formula (I), for example at an elevated temperature in the range from 50°C to 120°C, preferably in the presence of a base such as triethylamine.

In a further example, the reaction between the compound of formula (II) wherein R^a is OH and the reagent of the abovedefined formula (IIIA) may be carried out in an aprotic solvent, such as dimethylformamide, at a low to an elevated temperature, for example in the range from 50°C to 120°C, for example at 80°C, and preferably in the presence of a base, such as sodium hydride. In an alternative aspect, when R^y in the compound of formula (IIIA) represents H and R^a is OH in the compound of formula (II), then a suitable reagent is provided by diethylazodicarboxylate and triphenylphosphine; the coupling reaction may be carried out in any suitable solvent at a low to medium temperature, for example in tetrahydrofuran at a temperature in the range of between 0 and 60°C.

A compound of formula (II), wherein $A^{3'}$ represents a moiety of formula $-(CH_2)_m-CH(OR^{1'})-$, may be prepared by reacting a source of a carbene of formula (IV):



(IV)

wherein A^2, Y and m are as defined in relation to the compound of formula (I), R^b is a moiety R^a or a moiety convertible to a moiety R^a and R^9 is the above defined $R^{2'}$ or a protecting group, with a compound of formula (V):

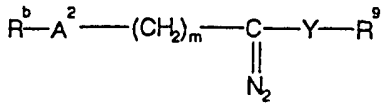
$$R^{1'}OH$$

(V)

wherein $R^{1'}$ is defined in relation to formula (II); and thereafter, if required, converting a moiety R^b into a moiety R^a and removing any protecting group.

Preferably, Y is CO. Preferably, R^9 is $OR^{3'}$ or $-NR^4R^5$.

A suitable source of the carbene of formula (IV) is provided by reacting a compound of formula (IVA):



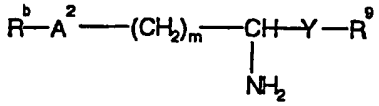
(IVA)

wherein A^2, R^9, R^b, Y and m are as defined in relation to formula (IV), with a suitable catalyst such as a rhodium (II) salt, for example rhodium (II) acetate, or a copper(II) salt, such as $Cu(Cl)_2$, or copper powder.

The conditions used in the preparation of the carbene of formula (IV) from (IVA) will of course depend upon the particular carbene chosen, but in general conventional procedures are used, for example when (IV) is the carbene and (IVA) is the source of carbene then suitable conditions are analogous to those disclosed in Tetrahedron Lett. 1973, 2233.

The reaction between the carbene of formula (IV) and the compound of formula (V) may be carried out under conventional conditions, generally in an inert solvent, such as benzene, or when practicable in compound (V) as solvent, at any temperature providing a convenient rate of formation of the required product, generally at an elevated temperature, such as the reflux temperature of the solvent: Suitably, the conditions used are analogous to those disclosed in Tetrahedron Lett., 1973, 2233.

When the source of the carbene is a compound of formula (IVA), the compound of formula (IVA) may be prepared by diazotizing a compound of formula (VI):



(VI)

wherein A^2, R^9, R^b, Y and m are as defined in relation to the compound of formula (IV), with an appropriate diazotizing agent; and thereafter, if required, converting a moiety R^b into a moiety R^a and removing any protecting group.

A suitable diazotizing agent is an alkyl nitrite, such as iso-amyl nitrite.

Suitable diazotising conditions for preparing the compound of formula (IVA) are conventional conditions, for example those disclosed in Tetrahedron Lett., 1971, 4495.

Any moiety R^b may be converted into a moiety R^a by the appropriate conventional means, for example when R^b represents -OH and R^a represents $HX\text{-}(CH_2)_n\text{-}O$- the appropriate conversion may be carried out by coupling a compound of formula (VI) wherein R^b is OH with a compound of formula (g):

$$R^z\text{-}X\text{-}(CH_2)_n\text{-}OH \qquad (g)$$

wherein X and n are as defined in relation to formula (I) and R^z is a protecting group and thereafter, if necessary, removing any protecting group.

The last abovementioned reaction is generally carried out in the presence of a suitable coupling agent; a suitable coupling agent being diethylazodicarboxylate and triphenylphosphine. The coupling reaction may be carried out in any suitable solvent at a low to medium temperature, for example in tetrahydrofuran at a temperature in the range of between 0 and 60°C.

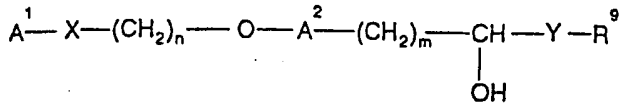
Generally, for the preparation of compounds of formula (II), wherein R^a is OH, from compounds of formula (IV), R^b in (IV) is either OH or a suitably protected OH, such as a silylated OH.

The compounds of formula (V) are known commercially available compounds or they may be prepared using methods analogous to those used to prepare such compounds.

The compounds of formula (VI) are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in Tetrahedron Lett., 1971, 4495, in particular the compound wherein R^9 is OCH_3, m is 1, A^2 is 1,4-phenylene and R^b is OH is a commercially available compound.

The compounds of formula (g) are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in EP0356214.

A compound of formula (I), wherein A^3 represents a moiety of formula $-(CH_2)_m\text{-}CH(OR^1)$-, or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be prepared by reacting an activated form of a compound of formula (VII):



(VII)

wherein A^1, A^2, X, Y, m and n are as defined in relation to formula (II) and R^9 is as defined in relation to formula (IV) with a compound of formula (VIII);

$$R^1 - L^1 \qquad \text{(VIII)}$$

wherein R^1 is as defined in relation to formula (I) and L^1 represents a leaving group or atom; and thereafter if required carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any protecting group; and

(iii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

Suitably, L^1 is a halogen atom, for example a bromine atom.

A suitable activated form of a compound of formula (VII) is an anionic form such as a salted form and especially an alkali metal salted form, for example a sodium salt.

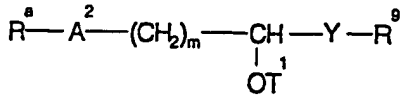
The activated form of the compound of formula (VII) may be prepared by any appropriate conventional procedure. For example, the anionic form of the compound of formula (VII) may be prepared by treating the compound of formula (VII) with a base, such as a metal hydride base, for example sodium hydride.

The reaction conditions for the reaction between the compounds of formulae (VII) and (VIII) are generally conventional alkylation conditions. For example the reaction between the salted form of a compound of formula (VII) and a compound of formula (VIII) may be carried out in an aprotic solvent, such

as dimethylformamide, at any temperature providing a suitable rate of formation of the required product, generally an elevated temperature such as in the range of 40°C to 100°C, for example 80°C.

Favourably, the formation of the activated form of (VII) from (VII) - for example the formation of a salted form of (VII) - may be carried out *in-situ* prior to the reaction of the activated form of (VII) with the above defined compound of formula (VIII).

A compound of formula (VII) may be prepared by reacting a compound of formula (IX):



(IX)

wherein R^a, R^9, A^2, Y and m are as defined above and T^1 is hydrogen or a hydroxyl protecting group, with an appropriate reagent capable of converting R^a to a moiety of the above defined formula (f).

The reagent capable of converting R^a to a moiety of formula (f) is as defined above in relation to the formation of a compound of formula (I) from a compound of formula (II).

Suitable values for R^a include those described hereinbefore.

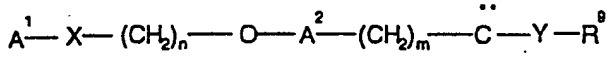
Suitable reaction conditions for the reaction of the compound of formula (IX) and the appropriate reagent include those described above in relation to the preparation of compound (II) with the said appropriate reagent.

Preferably, in the compound of formula (IX), R^a represents a hydroxyl group and a particularly appropriate reagent is the above defined compound of formula (IIIA).

The reaction between the compound of formula (IX), wherein R^a is an hydroxyl group, and the reagent of the abovedefined formula (IIIA) may be carried out in an aprotic solvent, such as dimethylformamide, at a low to an elevated temperature, for example in the range of from 50°C to 120°C, for example at 80°C, and preferably in the presence of a base, such as sodium hydride.

The compounds of formula (IX), wherein R^a is OH, are known compounds or they are compounds prepared by methods analogous to those used to prepare known compounds, for example those disclosed in Dictionary of Organic Compounds 5th Edition, Vol. 3, p.3222, Chapman & Hall, or D.H. Williams *et. al.* J.Chem.Soc., Section B, 1969, 439, or J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience or for example those disclosed in International Application, Publication No. WO92/02520.

A compound of formula (I), wherein A^3 represents a moiety of formula -$(CH_2)_m$-CH(OR^1)-, or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be prepared by reacting a source of a carbene of formula (X):



(X)

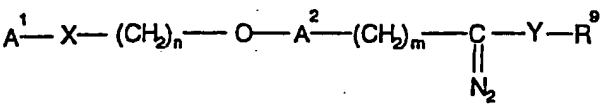
wherein A^1, A^2, X, Y, m and n are as defined in relation to formula (I) and R^9 is as defined in relation to formula (IV), with a compound of the above defined formula (V); and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any protecting group; and

(iii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

A suitable source of a carbene of formula (X) is provided be reacting a compound of formula (XI):



(XI)

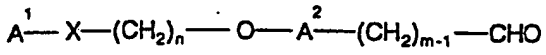
wherein A^1, A^2, R^9, X, Y, m and n are as defined in relation to formula (X) with a suitable catalyst such as a rhodium (II) salt, for example rhodium (II) acetate, or a copper(II) salt, such as $Cu(Cl)_2$, or copper powder.

The carbene of formula (X) may be prepared from the compound of formula (XI) by using an analogous procedure to that used for the preparation of the carbene of formula (IV) from the compound of formula (IVA).

The reaction conditions for the reaction between the compounds of formulae (X) and (V) are equivalent to those used in the reaction between the compounds of formulae (IV) and (V).

The compound of formula (XI) may be prepared by reaction between the compounds of formulae (IIIA) and (VI) using an analogous procedure to that used for the preparation of the compound of formula (I) from the compounds of formulae (II) and (IIIA) and thereafter diazotized as described above for the conversion of (VI) to (IVA).

A compound of formula (I) wherein A^3 represents a moiety of formula $-(CH_2)_{m-1}-CH=C(OR^1)-$ or $-(CH_2)_m-CH(OR^1)-$, or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be prepared by reacting a compound of formula (XII):



(XII)

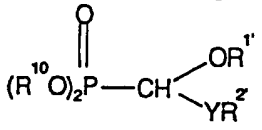
wherein A^1, A^2, X, m and n are as defined in relation to formula (I), with a reagent capable of converting the CHO carbon atom into a group of the above defined formula $CH=C(OR^1)-Y.R^2$; and thereafter, if required, reducing the group $-CH=C(OR^1)-$ to provide a compound wherein A^3 represents a moiety of formula $-(CH_2)_m-CHOR^1-$ and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any protecting group; and

(ii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

A suitable reagent capable of converting the CHO carbon atom into a group of the above defined formula -CH=C(OR^1)-Y.R^2 is a Wittig reagent or preferably a Wadsworth Emmons reagent of formula (XIII):



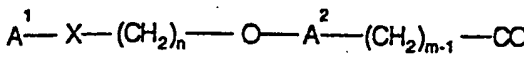
(XIII)

wherein R$^{1'}$, R$^{2'}$ and Y are as defined in relation to formula (II) and R^{10} represents a C_{1-6} alkyl group, preferably a methyl or ethyl group.

The reaction between the compounds of formulae (XII) and (XIII) may be carried out under conventional Wadsworth Emmons reaction conditions, for example in an aprotic solvent, such as tetrahydrofuran, at low to ambient temperature, such as in the range of from 0° to 25°C, conveniently at ambient temperature, preferably in an inert atmosphere and under anhydrous conditions. Preferably the compound of formula (XIII) is suitably activated, for example by the addition of a base such as sodium hydride or n-butyl lithium, prior to the addition of the compound of formula (XII).

The reduction of a compound wherein A^3 represents a moiety of formula -$(CH_2)_{m-1}$-CH=C(OR^1)- to provide a compound wherein A^3 represents a moiety of formula -$(CH_2)_m$-CH(OR^1)- may be carried out using conventional reduction methods, such as catalytic reduction using for example a 10% palladium-on-carbon catalyst in an alkanolic solvent such as ethanol, or by use of a metal/solvent system such as magnesium metal/methanol as described in Tet. Lett. 1986, 27, 2409.

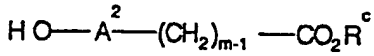
A compound of formula (XII) may be prepared from a compound of formula (XIIA):



(XIIA)

wherein A^1, A^2, X, m and n are as defined in relation to formula (I) and R^c represents hydrogen or a C_{1-6} alkyl group, suitably a methyl group, by conventional methods for converting an ester group into a carbonyl group; one convenient method involves reducing the ester group to give a primary alcohol using for example a metal hydride reducing agent such as lithium aluminium hydride in tetrahydrofuran, and thereafter oxidising the primary alcohol to give the required carbonyl group by use of an oxidising reagent such as pyridine-sulphur trioxide complex in dimethylsulphoxide.

A compound of formula (XIIA) may be prepared from a compound of formula (XIIB):

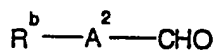


(XIIB)

wherein A^2, m and R^c are as defined in relation to formula (XIIA), with a compound of the above defined formula (IIIA).

Suitably reaction conditions for the reaction between the compounds of formulae (IIIA) and (XIIB) are those described above for the reaction between the compounds of formulae (II) and (IIIA).

A compound of formula (II) wherein $A^{3'}$ represents a moiety of formula $-CH=C(OR^{1'})-$ or $-CH_2-CH(OR^{1'})-$, or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be prepared by reacting a compound of formula (XIV):



(XIV)

wherein R^b and A^2 are as defined in relation to formula (IV), with a reagent capable of converting the CHO carbon atom into a group of the above defined formula $-CH=C(OR^{1'})-Y.R^{2'}$; and thereafter, if required, reducing the group $-CH=C(OR^{1'})-$ to provide a group of formula $-CH_2-CHOR^{1'}-$; and thereafter, if required, removing any protecting group.

Preferably, R^b is a protected OH group.

A suitable reagent capable of converting the CHO carbon atom of compound (XIV) into a group of the above defined formula

-CH=CH(OR$^{1'}$)-Y.R$^{2'}$ is a compound of the above defined formula (XIII) in optionally protected form as defined by the nature of R$^{1'}$ and R$^{2'}$ in the required compound of formula (II).

Suitable conditions for the reaction between the compound of formula (XIV) and the said reagent are analogous to those described above for the reaction between the compounds of formulae (XII) and (XIII).

The compounds of formula (XII), in particular those wherein m is 1, may also be prepared by methods disclosed in EP0306228.

The compounds of formula (XIIB) are known commercially available compounds or they are compounds prepared by analogous methods used to prepare such compounds or they may be prepared from such compounds, for example by converting a commercially available carboxylic acid into an alkyl ester.

The compounds of formula (XIII), are known compounds or they are compounds prepared by methods analogous to those used to prepare known compounds, for example those disclosed in Annalen Chemie 1966, *699*, 53 or J. Org. Chem. 1983, *48*, 3408 and Tetrahedron 1992, *48*, 3991.

The compounds of formulae (XIV) are known compounds or they are compounds prepared by methods analogous to those used to prepare known compounds, for example those disclosed in EP 0306228.

A compound of formula (I), wherein A^3 represents a moiety of formula -CH$_2$ - CH(OR^1)- wherein R^1 represents alkyl, or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be prepared by hydrolysing a compound of formula (XV):

$$A^1 - X - (CH_2)_n - O - A^2 - CH_2 - CH(OR^1) - CN \qquad (XV)$$

wherein A^1, A^2, R^1, X and n are as defined in relation to formula (I) to provide a compound of formula (I) wherein R^2 represents OH; and thereafter, if required, converting R^2 as OH into another R^2; and thereafter, if required,carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any protecting group; and

(iii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

The hydrolysis of the compound of formula (XV) may be carried out using conventional conditions and reagents for nitrile hydrolysis, for example basic hydrolysis using 10% sodium hydroxide in methanol.

The conversion of R^2 as OH into another R^2 may be effected by using any convenient method, such as those methods described hereinafter.

A compound of formula (XV) may be prepared from a compound of formula (XVI):

$$A^1 - X - (CH_2)_n - O - A^2 - CH_2 - CH(OR^{1a}) - OR^{1b} \qquad \text{(XVI)}$$

wherein A^1, A^2, X and n are as defined in relation to formula (I) and $R^{1a} = R^{1b}$ which represents alkyl; by reaction with trimethylsilylcyanide.

The reaction between the compounds of formulae (XVI) and trimethylsilylcyanide may be carried out in an inert solvent, such as dichloromethane, at low to ambient temperature, conveniently at ambient temperature and preferably in the presence of a Lewis acid catalyst, such as boron trifluoride etherate.

A compound of formula (XVI) may be prepared from a compound of formula (XVII):

$$A^1 - X - (CH_2)_n - O - A^2 - CH = CH - OR^{1a} \qquad \text{(XVII)}$$

wherein A^1, A^2, R^{1a}, X and n are as defined in relation to formula (XV); by reaction with a compound of formula (XVIII):

$$R^{1a}\text{-}OH \qquad \text{(XVIII)}$$

wherein R^{1a} is as defined above.

The reaction between the compounds of formulae (XVII) and (XVIII) is suitably carried out using the compound of formula (XVIII) as solvent, generally at an elevated temperature such as the reflux temperature of the solvent and preferably in the presence of p-toluenesulphonic acid.

Preferably, R^{1a} is methyl.

A compound of formula (XVII) may be prepared by reaction of the above defined compound of formula (XII), wherein m is 1, with a reagent capable of converting the CHO carbon atom of formula (XII) into a group of the above defined formula -CH=CH - OR^1, the reagent being suitably a Wittig reagent of formula (XIX):

$$[Ph_3PCH_2 - OR^1]^+ \ Cl^- \qquad \text{(XIX)}$$

wherein R^1 is as defined in relation to formula (I).

The reaction between the compounds of formulae (XII) and (XIX) may be carried out under conventional Wittig reaction conditions, for example in an aprotic solvent, such as tetrahydrofuran, at low to ambient temperature, such as in the range of from -10° to 25°C, conveniently at ambient temperature and, preferably, in an inert atmosphere under anhydrous conditions. Preferably, the compound of formula (XIX) is suitably activated by, for example, the addition of a base such as sodium hydride, n-butyl lithium or lithium diisopropylamide, prior to the addition of the compound of formula (XII).

The compounds of formula (XVIII) and (XIX) are known compounds or they are compounds prepared by methods analogous to those used to prepare known compounds, for example those disclosed in J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.

A compound of formula (I), wherein A^3 is $(CH_2)_m$-CH(OR^1)- and R^2 is a C-linked aromatic heterocyclyl group, or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, may be prepared by reacting a compound of the above defined formula (XII) with an activated form of a compound of formula (XX)

(XX)

wherein het-CH is an aromatic heterocyclic group represented by R^2 which contains at least 1 carbon atom and thereafter converting the compound wherein R^1 is hydrogen into another R^1 ; and thereafter if required:

(i) converting a compound of formula (I) to a further compound of formula (I);

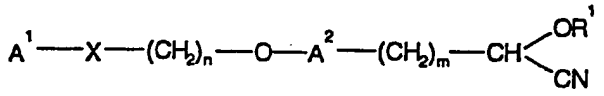
(ii) removing any necessary protecting group;

(iii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

A suitable activated form of a compound of formula (XX) is a salted form such as a lithium salted form.

The activated form of a compound of formula (XX) may be prepared by reacting an aromatic heterocyclic group Het-CH or Het-CL, wherein L is a leaving group such as halogen, with an appropriate, conventional activating agent such as a salting agent, for example an alkyl lithium, in an aprotic solvent such as tetrahydrofuran according to known methods and procedures for example those disclosed in Adv. Heterocyclic chem., 1993, 56, 155.

Compounds of formula (I) wherein A^3 is $(CH_2)_m$-CH(OR^1)- and R^2 is a C-linked tetrazolyl group or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein the heterocyclyl group may be prepared by reacting a compound of formula (XXI)



(XXI)

wherein A^1, A^2, R^1, X, m and n are as defined in relation to formula (I), with a source of azide ions such as an azide salt, suitably an alkali metal azide, for example sodium azide.

The compound of formula (XXI) may be prepared by dehydrating a compound of formula (I) wherein A^3 is $(CH_2)_m$-CH(OR^1) and YR^2 is $CONH_2$ using for example $POCl_3$.

The reaction between the compound of formula (XXI) and the source of azide ions may be carried out under conventional conditions for example when sodium azide is the source of azide ions the reaction may be effected in an aprotic solvent such as dimethylformamide generally at an elevated temperature, for example the reflux temperature of the solvent; preferably in the presence of trimethylsilyl chloride.

The abovementioned conversion of a compound of formula (I) into a further compound of formula (I) includes:

a) converting one group R into another group R ;

b) converting one group OR^1 into another group OR^1 ;

c) converting one group $Y.R^2$ wherein Y is CO into another group $Y.R^2$;

d) converting one group $CO.R^2$ into another group $CS.R^2$; and

e) reducing a group -CH=C(OR^1)- to a group -CH_2-CH(OR^1)-.

The abovementioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

The conversion of a compound of formula (I) to a further compound of formula (I) may be carried out by using any appropriate conventional procedure.

Suitable conversions of one group R into another group R include converting a group R which represents hydrogen into a group R which represents an acyl group; such conversion may be carried out using an appropriate conventional acylation procedure, for example treating an appropriately protected compound of formula (I) with an acylating agent. Thus acetic anhydride may be used to prepare the compound of formula (I) wherein R is acetyl.

The above mentioned reduction may be carried out using any conventional reduction method, for example using boronhydride reducing agents, such as sodium borohydride in a solvent such as methanol.

Suitable conversions of one group $Y.R^2$ wherein Y is CO into another group $Y.R^2$, include:

(i) hydrolysing one group $Y.OR^{3a}$ wherein R^{3a} is alkyl, aryl or aralkyl into a group Y.OH, wherein Y is CO;

(ii) aminating one group $Y.R^{2b}$ wherein R^{2b} is alkoxy into a group $Y.NR^4R^5$,wherein Y is CO;

(iii) halogenating the above defined group Y.OH to provide the corresponding acid halide, and then aminating the halide to provide the abovementioned group $Y.NR^4R^5$ wherein Y is CO;

(iv) esterifying a group YOH to give a group Y-Oalkyl or Y-Oaralkyl, wherein Y is CO; and

(v) converting one group $Y.NH_2$ wherein Y is CO into a group Y-C-Het wherein Y is a bond and C-Het is a C-linked aromatic heterocyclyl group.

Suitable hydrolysis methods for use in conversion c(i) are conventional ester hydrolysis methods, for example using an alkali hydroxide in aqueous methanol.

Suitable amination methods for conversion c(ii) or c(iii) include conventional methods, for example treatment with aqueous ammonia in tetrahydrofuran/methanol.

Suitable halogenation methods for conversion c(iii) include conventional methods, for example treatment with oxalyl chloride.

Suitable esterification methods for conversion c(iv) are conventional methods, thus alkyl esters may be prepared by using the appropriate alkanol, for example methanol, in the presence of an acid and aralkyl esters may be prepared by treatment of a salted YOH group, such as a sodium salt, with an appropriate aralkyl halide, for example benzyl bromide.

Suitable conversion of a group $Y.NH_2$ wherein Y is CO into a group Y-C-Het wherein Y is a bond and C-Het is a C-linked aromatic heterocyclyl group includes:

a) reaction with a hydrazine, for example hydrazine hydrate, and an amide acetal, such as dimethylformamide dimethyl acetal, to provide a 1,2,4-triazole; or

b) reaction with a hydroxylamine, for example hydroxylamine hydrochloride, and an amide acetal, such as dimethylformamide dimethyl acetal, to provide a 1,2,4-oxadiazole.

Suitable conversions of one group $CO.R^2$ into another group $CS.R^2$ may be effected using conventional methods,for example by using Lawesson's reagent in a solvent such as toluene, at any temperature providing an acceptable rate of formation of the required product, conveniently at the reflux temperature of the solvent.

Suitable reductions of one group $-CH=C(OR^1)-$ to a group $-CH_2CH(OR^1)-$ may be carried out using any convenient reduction procedure,

such as the catalytic reduction or metal/solvent reduction methods as described hereinbefore.

It will be appreciated that in any of the abovementioned reaction including the abovementioned conversions (a), (b), (c), (d) and (e) any reactive group in the substrate molecule may be protected, according to conventional chemical practice.

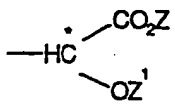
Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art. Thus, for example, suitable hydroxyl protecting groups include benzyl or trialkylsilyl groups.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

However for certain compounds of formula (I) there is provided a novel process for separating optical isomers of such compounds. Indeed the newly discovered process is considered to be capable of separating optical isomers of any compound providing the chiral carbon of such compound is attached to a carboxy ester group and a group OZ^1 wherein Z^1 is alkyl, aryl or aralkyl.

Accordingly, the present invention provides a process for separating optical isomers of a compound (the substrate ester) which comprises a moiety of formula (H):



(H)

wherein C* is a chiral carbon, Z is a C_{1-12} alkyl group and Z^1 is a C_{1-12} alkyl, aryl or an aryl C_{1-12} alkyl group,

which process comprises enantioselectively hydrolysing the ester group CO_2Z of one enantiomer into a carboxyl group with a lipase from Rhizopus delemar, Rhizopus arrhizus, Rhizopus LIP F4 or a lipase from Mucor miehei; and thereafter, as necessary, isolating either the enantiomerically enriched product carboxylic acid or the enanatiomerically enriched substrate ester.

The enantiomerically enriched product carboxylic acid and/or the enanatiomerically enriched substrate ester may be isolated using conventional extraction methods, such as phase separation and/or extraction into a suitable solvent, and thereafter, if required it may be chromatographed.

In an alternative isolation procedure, prior to isolation, the enantiomerically enriched substrate ester, may be converted by hydrolysis into the respective carboxylic acid which may then be isolated in the usual way. In one convenient aspect of the invention the enantiomerically enriched substrate ester may be hydrolysed by treatment with the abovementioned lipases to give the respective carboxylic acid.

The compounds of formula (I) which fall within formula (H) are those compounds wherein Z represents R^3 and Z^1 represents R^1: Thus the novel process may be used to prepare enantiomerically enriched compounds of formula (I) wherein A^3 represents $(CH_2)_m$-$CH(OR^1)$-, Y represents CO, R^2 is OR^3 and A^1, A^2, R^1, R^3 X, m and n are as defined in relation to formula (I)- (hereinafter referred to as compounds of formula (IA)).

The microbial lipase enzymes may be obtained by conventional culturing techniques such as those disclosed in J. Bacteriol., 1982, Vol.150 498-505. H. Gilbert and M. Tully, European Patent Application No. 0198440 and British Patent No. 1,474,519. The lipase may be isolated as a pure enzyme or, in the alternative a suitable source of the lipase may be incorporated into the reaction.

Preferably, the microbial lipase enzymes are obtained commercially as purified or partially purified enzyme preparations.

The hydrolysis of the compound of formula (H) may be carried out in any suitable aqueous solvent having controlled pH, for example in an aqueous buffer or in a solvent wherein the pH is controlled by the addition of aqueous sodium hydroxide, at a pH which provides a suitable rate of formation of the required product, which is generally a pH in the range of from 5 to 9, such as in the range of from 6 to 8, for example at pH7.

The hydrolysis may be carried out at any temperature which provides a suitable rate of formation of the required product, being generally at a low to ambient temperature, such as a temperature in the range of from 5°C to 40°C, such as in the range of from 20°C to 40°C and preferably in the range of from 20°C to 30°C, for example 23°C.

Generally, the substrate mixture is introduced into the reaction system as a solution in an organic solvent which may be a water miscible solvent such as acetone, tetrahydrofuran, dimethylsulphoxide, dimethylformamide or acetonitrile.

The stereoselective process selectively hydrolyses the compound (IA) having the same stereochemistry at the asterisked carbon atom as the equivalent carbon atom in (-) 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-methoxypropanoic acid.

The reaction conditions, such as the particular acidic pH and the reaction temperature which provide optimum enrichment for any particular enantiomerically enriched compound (H) may be determined by routine experimentation.

Suitably, the stereoselective reaction provides enantiomerically enriched compound (IA) in the form wherein the required enantiomer is present in greater than 70% w/w; and favourably greater than 80% w/w. Most favourably, the product from the stereoselective process provides enantiomerically enriched compound (IA) in the form wherein the required enantiomer is present as 80-100% w/w, preferably 90-100%, such as 90-95%, and most preferably 95-100%, for example 95%, 96%, 97%, 98%, 99% or 100% w/w.

The above mentioned enantiomerically enriched compound (IA) is considered to form a further aspect of the present invention. Accordingly the present invention provides enantiomerically enriched compound (IA) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

The present invention also provides enantiomerically enriched compound (IA) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein the required isomer is present in greater than 50% w/w; suitably greater than 70% w/w and favourably greater than 80% w/w. Most favourably, the enantiomerically enriched compound (IA) is in a form wherein 80-100% w/w , preferably 90-100%, such as 90-95%, and most preferably 95-100%, for example 95%, 96%,

97%, 98%, 99% or 100% w/w is in the form of the required isomer of a compound of formula (IA).

In one preferred aspect there is provided a compound of formula (IA) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, preferably in optically pure form.

The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties: The present invention accordingly provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

In a further aspect the present invention also provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

As indicated hereinbefore the present invention also provides a compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

Cardiovascular disease includes in particular atherosclerosis.

Certain eating disorders include in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating ,such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia.

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a tautomeric

form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate or sodium lauryl sulphate.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycaemic human or non-human mammal in need thereof.

The present invention further provides a method for the treatment of hyperlipidaemia in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a

pharmaceutically acceptable solvate thereof, to a hyperlipidaemic human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of hyperglycaemic humans, and/or the treatment and/or prophylaxis of hyperlipidaemic human, the compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In the treatment and/or prophylaxis of hyperglycaemic non-human mammals, especially dogs, the active ingredient may be adminstered by mouth, usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemia in non-human mammals.

The dosages regimens for the treatment of hypertension, cardiovascular disease and eating disorders will generally be those mentioned above in relation to hyperglycaemia.

In a further aspect the present invention provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

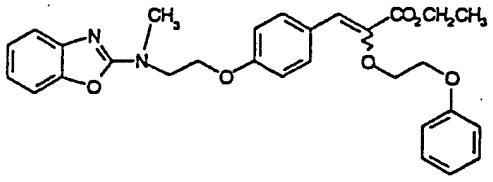
The present invention also provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders.

No toxicological effects have been established for the compounds of formula (I) in the abovementioned dosage ranges.

The following Procedures and Examples illustrate the invention but do not limit it in any way.

Example 1

Ethyl (E/Z)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-phenoxyethoxy)propenoate



A solution of triethyl 2-(2-phenoxyethoxy)phosphonoacetate (4.86 g) in dry tetrahydrofuran (50 mL) was added slowly to a stirred, ice-cooled suspension of sodium hydride (60% dispersion in oil; 0.60 g) in dry tetrahydrofuran (25 mL) under an argon atmosphere. The mixture was stirred at 0°C for 30 minutes prior to the addition of a solution of 4-[2-[N-(2-benzoxazolyl)-N-methylamino]-ethoxy]benzaldehyde (*Eur. Patent Appl., Publication No.* 0306228) (4.00 g) in dry tetrahydrofuran (50 mL). The mixture was allowed to warm to room temperature and stirred for a further 22 hrs. The solvent was evaporated and the residue suspended in water (700 mL) and extracted with ethyl acetate (3x500 mL). The combined ethyl acetate layers were washed with water (1L), brine (500 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with 2% ethyl acetate in dichloromethane as eluent to afford the title compound, a gum, as a mixture of double bond isomers which were only partially separated by chromatography. These were recombined to afford a 71:29 Z:E mixture, used directly in the next stage. [Found C, 69.3; H, 6.05; N, 5.7%; M^+ (EI) 502.2103. Calculated for $C_{29}H_{30}N_2O_6$ C, 69.3; H, 6.0; N, 5.6%; M^+ 502.2104].

^1H NMR δ ($CDCl_3$)

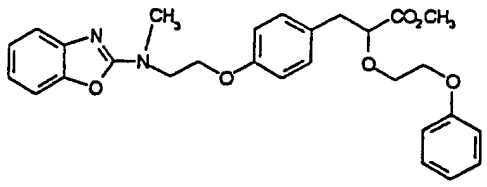
Z-Isomer: 1.35 (3H, t); 3.34 (3H, s); 3.95 (2H, t); 4.30 (8H, complex); 6.79-7.40 (12H, complex) and 7.79 (2H, d).

E-Isomer: 1.13 (3H, t); 3.34 (3H, s); 3.95 (2H, t); 4.10-4.40 (8H, complex); 6.23 (1H, s) and 6.70-7.40 (13H, complex).

The assignment of the major isomer as Z is by analogy with reported chemical shifts of similar olefinic protons (cf R. A. Aitken and G. L. Thom, *Synthesis*, 1989, 958).

Example 2

Methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-phenoxyethoxy)propanoate



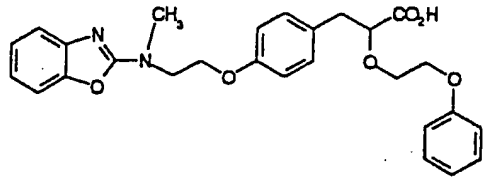
Magnesium turnings (1.0 g) were added to a mixture of ethyl (E/Z)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-phenoxyethoxy)-propenoate (4.51 g) and a crystal of iodine dissolved in methanol (150 mL) at room temperature. The mixture was stirred with slight warming until reaction ensued, at which point the heating was stopped and the mixture stirred at room temperature during the addition, over *ca* 5 minutes, of a further portion of magnesium (5.50 g). The reaction mixture was immersed in a cold water bath and stirring continued for 19 hrs then the mixture was evaporated *in vacuo*. The residue was suspended in water (500 mL) and stirred vigorously during the addition of concentrated hydrochloric acid to give (once *all* the suspension had dissolved) a final pH of 2.5. The mixture was extracted with ethyl acetate 2x500 mL) and the combined ethyl acetate layers then washed with water (800 mL), brine (500 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with 2% ethyl acetate in dichloromethane as eluent to afford the title compound, a gum, which was used directly in the next stage. [Found M^+ (EI) 490.2105. Calculated for $C_{28}H_{30}N_2O_6$ M^+ 490.2104].

^{1}H NMR δ ($CDCl_3$)

2.99 (2H, m); 3.34 (3H, s); 3.67 (3H, s); 3.68 (1H, m); 3.92 (3H, complex); 4.03 (2H, m); 4.20 (3H, complex) and 6.72-7.37 (13H, complex).

Example 3

3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-phenoxyethoxy)propanoic acid



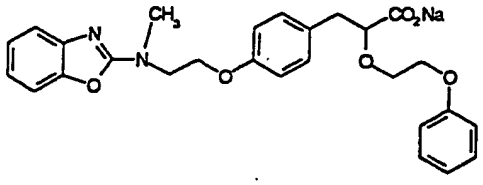
A mixture of methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-phenyl]-2-(2-phenoxyethoxy)propanoate (3.36 g), 10% aqueous sodium hydroxide solution (20 mL) and methanol (30 mL) was stirred for 3 hrs at room temperature, concentrated and then diluted with water (500 mL) and acidified to pH2 with concentrated hydrochloric acid. The mixture was extracted with ethyl acetate (3x400 mL) and the combined ethyl acetate solutions washed with water (1 L) and brine (500 mL), dried ($MgSO_4$) and evaporated to afford the title compound, a gum, which was used directly in the salt forming stage.

^{1}H NMR δ ($CDCl_3$)

2.95 (1H, dd); 3.13 (1H, dd); 3.32 (3H, s); 3.75-4.20 (9H, complex); 4.75 (1H, broad, exchanges with D_2O) and 6.70-7.40 (13H, complex).

Example 4

3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-phenoxyethoxy)propanoic acid, sodium salt



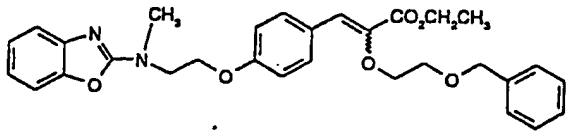
Sodium hydride (60% dispersion in mineral oil, 0.12 g) was added to a stirred solution of 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-phenoxyethoxy)propanoic acid (1.30 g) in methanol (20 mL). The mixture was stirred at room temperature for 1 hr, concentrated *in vacuo* and diluted with diethyl ether (50 mL). The resulting solid was filtered and dried to afford the title compound, mp 60-62°C. [Found MH^+ of free acid (FAB) 477.2056. Calculated for free acid ($M = C_{27}H_{28}N_2O_6$) MH^+ 477.2025].

^{1}H NMR δ (DMSO-d_6)

2.65 (1H, dd); 2.88 (1H, dd); 3.22 (3H, s); 3.46 (1H, m); 3.60 (1H, dd); 3.87 (3H, complex); 3.93 (2H, m); 4.18 (2H,t) and 6.70-7.40 (13H, complex).

Example 5

Ethyl (E/Z)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-benzyloxyethoxy)propenoate



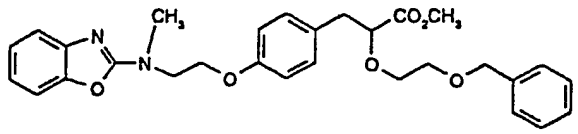
The title compound, a gum, was obtained as a 72:28 mixture of Z and E double bond isomers when triethyl 2-(2-benzyloxyethoxy)phosphonoacetate was reacted with 4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]benzaldehyde in a manner similar to that described in Example 1. The double bond isomers were only partially separated by chromatography on silica gel with 2.5% ethyl acetate in dichloromethane as eluent and were recombined for use in the next stage. [Found M^+ (EI) 516.2259. Calculated for $C_{30}H_{32}N_2O_6$ M^+ 516.2260].

^{1}H NMR δ ($CDCl_3$)

Z-Isomer: 1.34 (3H, t); 3.33 (3H, s); 3.77 (2H, m); 3.93 (2H, t); 4.13 (2H, m); 4.20 (2H, t); 4.27 (2H, q); 4.53 (2H, s); 6.71 (2H, d); 6.96 (1H, s); 6.97-7.40 (9H, complex) and 7.79 (2H, d).
E-Isomer: 1.13 (3H, t); 3.34 (3H, s); 3.75-4.65 (12H, complex); 6.15 (1H, s); 6.75 (2H, d) and 6.90-7.90 (11H, complex).

Example 6

Methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-benzyloxyethoxy)propanoate



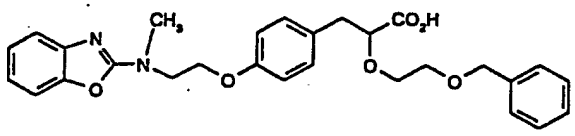
The title compound, a gum, was prepared from ethyl (E/Z)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-benzyloxyethoxy)propenoate in a manner similar to that described for Example 2. [Found M^+ (EI) 504.2261. Calculated for $C_{29}H_{32}N_2O_6$ M^+ 504.2261].

^1H NMR δ ($CDCl_3$)

2.95 (2H, complex); 3.33 (3H, s); 3.40-3.80 (4H, complex); 3.67 (3H, s); 3.92 (2H, t); 4.10 (1H, t); 4.19 (2H, t); 4.45 (2H, s); 6.77 (2H, d) and 6.95-7.40 (11H, complex).

Example 7

3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-benzyloxyethoxy)propanoic acid



The title compound, a gum, was prepared from methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-benzyloxyethoxy)propanoate by a procedure similar to that described for Example 3. [Found MH^+ (CI) 491.2180. Calculated for $C_{28}H_{30}N_2O_6$ MH^+ 491.2182].

^1H NMR δ ($CDCl_3$)

2.95 (1H, m); 3.15 (1H, m); 3.32 (3H, s); 3.50-3.70 (4H, m); 3.90 (2H, t); 4.07 (1H, m); 4.17 (2H, t); 4.52 (2H, s); 6.50 (1H, br, exchanges with D_2O) and 6.95-7.45 (13H, complex).

DEMONSTRATION OF EFFICACY OF COMPOUNDS

Obese Mice, Oral Glucose Tolerance Test.

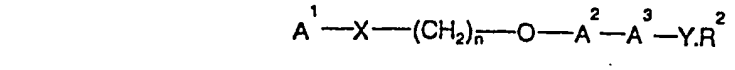
C57bl1/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powered oxoid diet containing the test compound. After 8 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3g/kg). Blood samples for glucose analysis were taken 0,45,90 and 135 minutes after glucose administration and the results appear below as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control group. 8 mice were used for each treatment.

Table

Example No.	Level in diet ($\mu mol.kg^{-1}$ of diet)	% Reduction in area under blood glucose curve
4	100	61

CLAIMS/A

1. A compound of formula (I):



(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

A^2 represents a benzene ring having three optional substituents;

A^3 represents a moiety of formula $-(CH_2)_m-CH(OR^1)-$ wherein m represents an integer in the range of from 1 to 5 and R^1 represents a moiety $-(CH_2)_x-Y^1-(CH_2)_y-T$ wherein Y^1 represents O, NR° wherein R° is H, alkyl or alkylcarbonyl or Y^1 is S, T represents a phenyl group optionally substituted with up to 3 substituents selected from halo, alkyl and alkoxy, x represents an integer in the range of from 2 to 5 and y represents zero or an integer in the range of from 1 to 5; or

A^3 represents a moiety of formula $-(CH_2)_{m-1}-CH=C(OR^1)-$ wherein R^1 and m are as defined above;

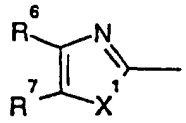
R^2 represents OR^3 wherein R^3 represents hydrogen, alkyl, aryl or aralkyl or R^2 represents an aromatic heterocyclyl group or $-NR^4R^5$ wherein R^4 and R^5 each independently represent hydrogen, alkyl or alkylcarbonyl or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring, providing that R^2 represents an aromatic heterocyclyl group only when Y as defined below represents a bond ;

X represents NR wherein R represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

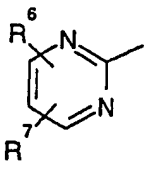
Y represents C=O or C=S or a bond providing that Y represents a bond only when R^2 represents the above mentioned aromatic heterocyclyl group; and

n represents an integer in the range of from 2 to 6.

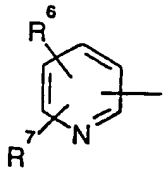
2. A compound according to claim 1, wherein A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

wherein:
R^6 and R^7 each independently represents a hydrogen or halogen atom, an alkyl or alkoxy group or a substituted or unsubstituted aryl group or when R^6 and R^7 are each attached to adjacent carbon atoms, then R^6 and R^7 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^6 and R^7 together is substituted or unsubstituted; and in the moiety of formula (a) X^1 represents oxygen or sulphur.

3. A compound according to claim 1 or claim 2, wherein A3 represents a moiety of formula $-(CH_2)_m-CH(OR^1)-T$ wherein R^1, T and m are as defined in relation to claim 1.

4. A compound according to any one of claims 1 to 3, wherein R^1 is a moiety of formula $-CH_2-CH_2-Ph$.

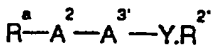
5. A compound according to any one of claims 1 to 4, wherein R^2 represents OR^3 in which R^3 represents hydrogen or alkyl.

6. A compound according to any one of claims 1 to 5, wherein m is 1 and n is 2.

7. A compound according to any one of the examples 1 to7 described herein, or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof.

8. A process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, which process comprises:

a) reacting a compound of formula (II):



(II)

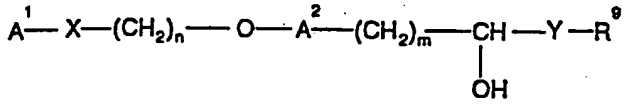
wherein A^2 and Y are as defined in relation to formula (I);
$A^{3'}$ represents a moiety of formula $-(CH_2)_m-CH(OR^{1'})-$ wherein $R^{1'}$ represents R^1 as defined in relation to formula (I) or a protected form thereof, and m is as defined in relation to formula (I), or A^3 represents a moiety of formula $-(CH_2)_{m-1}-CH=C(OR^{1'})-$ wherein $R^{1'}$ is as defined above;
$R^{2'}$ represents R^2 as defined in relation to formula (1) or a protected form thereof and R^a is a moiety convertible to a moiety of formula (f):

$$A^1\text{-}X\text{-}(CH_2)_n\text{-}O- \qquad (f)$$

wherein A^1, X and n are as defined in relation to formula (I);
with an appropriate reagent capable of converting R^a to the said moiety (f):

(b) for a compound of formula (I) wherein A^3 represents a moiety of formula $-(CH_2)_m-CH(OR^1)-$:

(i) by reacting an activated form of a compound of formula (VII):



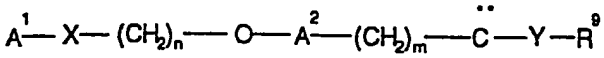
(VII)

wherein A^1, A^2, X, Y, m and n are as defined in relation to formula (II) and R^9 R^9 is $R^{2'}$ as defined above or a protecting group, with a compound of formula (VIII);

$$R^1 - L^1 \qquad \text{(VIII)}$$

wherein R^1 is as defined in relation to formula (I) and L^1 represents a leaving group or atom; or

(ii) by reacting a source of a carbene of formula (X):



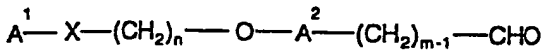
(X)

wherein A^1, A^2, X, Y, m and n are as defined in relation to formula (I) and R^9 is $R^{2'}$ as defined above or a protecting group, with a compound of the above defined formula (V):

$$R^{1'}OH \qquad \text{(V)}$$

wherein $R^{1'}$ is defined in relation to formula (II);

(c) for a compound of formula (I) wherein A^3 represents a moiety of formula $-(CH_2)_{m-1}-CH=C(OR^1)-$ or $-(CH_2)_m-CH(OR^1)-$, by reacting a compound of formula (XII):



(XII)

wherein A^1, A^2, X, m and n are as defined in relation to formula (I), with a reagent capable of converting the CHO carbon atom into a group of the above defined formula $CH=C(OR^1)-Y.R^2$; and thereafter, if required, reducing the group $-CH=C(OR^1)-$ to provide a compound wherein A^3 represents a moiety of formula $-(CH_2)_m-CHOR^1-$;

(d) for a compound of formula (I) wherein A^3 represents a moiety of formula $-CH_2 - CH(OR^1)-$ wherein R^1 represents alkyl, by hydrolysing a compound of formula (XV):

$$A^1 - X - (CH_2)_n - O - A^2 - CH_2 - CH(OR^1) - CN \qquad (XV)$$

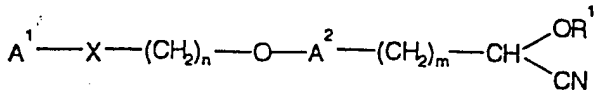
wherein A^1, A^2, R^1, X and n are as defined in relation to formula (I) to provide a compound of formula (I) wherein R^2 represents OH; and thereafter, if required, converting R^2 as OH into another R^2;

(e) for a compound of formula (I) wherein A^3 is $(CH_2)_m-CH(OR^1)-$ and R^2 is a C-linked aromatic heterocyclyl group, by reacting a compound of the above defined formula (XII) with an activated form of a compound of formula (XX)

(XX)

wherein het-CH is an aromatic heterocyclic group represented by R^2 which contains at least 1 carbon atom and thereafter converting the compound wherein R^1 is hydrogen into another R^1;

(f) for a compound of formula (I) wherein A^3 is $(CH_2)_m-CH(OR^1)-$ and R^2 is a C-linked tetrazolyl group, wherein the heterocyclyl group by reacting a compound of formula (XXI)



(XXI)

wherein A^1, A^2, R^1, X, m and n are as defined in relation to formula (I), with a source of azide ions; and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

9. A pharmaceutical composition comprising a compound of formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

10. A compound of formula (I), or tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

11. A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease and/or certain eating disorders.

12. A method for the treatment and/or prophylaxis of hyperglycaemia hyperlipidaemia, hypertension, cardiovascular disease and/or certain eating disorders in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a

pharmaceutically acceptable solvate thereof to a hyperglycaemic human or non-human mammal in need thereof.

13. The use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease and/or certain eating disorders.

INTERNATIONAL SEARCH REPORT

In uonal Application No
PCT/EP 94/04112

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/58 C07D213/74 C07D239/42 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 19702 (PFIZER INC.) 26 December 1991 see claims	1,2,9-13
A	WO,A,92 02520 (BEECHAM GROUP PLC) 20 February 1992 see claims	1,2,9-13
P,X	WO,A,94 01420 (SMITHKLINE BEECHAM CORPORATION) 20 January 1994 see claims	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 February 1995	22. 02. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir. ational application No.
PCT/EP 94/04112

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 12 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The definition of radicals A1 and R2 as aromatic heterocyclic group is too broadly formulated to permit an adequate search. The search has essentially been limited to the compounds of formula I which are supported by the examples. (Claim 1 has been searched incompletely)

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

In .tional Application No
PCT/EP 94/04112

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9119702	26-12-91	US-A-	5089514	18-02-92
		AU-B-	646052	03-02-94
		AU-A-	7995691	07-01-92
		EP-A-	0533781	31-03-93
		HU-A-	65603	28-07-94
		US-A-	5306726	26-04-94
WO-A-9202520	20-02-92	AU-B-	646491	24-02-94
		AU-A-	8317891	02-03-92
		CA-A-	2093146	07-02-92
		EP-A-	0542816	26-05-93
		JP-T-	6500538	20-01-94
		NZ-A-	239265	25-02-94
WO-A-9401420	20-01-94	AU-B-	4506893	31-01-94